Eyler Yvonn
09/016074

7) Pattison et al.
"The RANTES chemokine. A new target for immunomodulatory therapy?"
CLINICAL IMMUNOTHERAPEUTICS
Vol. 4 (1)
p. 1-8
1995

8) Mule et al.
"RANTES secretion by gene-modified tumor cells results in loss of tumorigenicity in vivo..."
HUMAN GENE THERAPY
vOL. 7 (13)
P. 1545-1553
1996

9) Cardoso et al.
"Lymphoblastic leukemia cells express CXCR-4 and migrate through endothelium in response to SDF-1..."
BLOOD
Vol. 92 (10 suppl. 1 part 1-2)
p. 618A
Nov. 15, 1998

10) Schall, T.
"Fractalkine--a strange attractor in the chemokine landscape"
IMMUNOLOGY TODAY
Vol. 18 (4)
p. 147-?
1997

11) Dilloo et al.
"combined chemokine and cytokine gene transfer enhances antitumor immunity"
NATURE MEDICINE
Vol. 2 (10)
p. 1090-1095
1996

12) Tannenbaum et al.
"Anti-tumor functions of IP-10 and Mig"
JOURNAL OF LEUKOCYTE BIOLOGY
Suppl
p. 18-?
1997

13) Oppenheim et al.
"Prospects for cytokine and chemokine biotherapy"
CLINICAL CANCER RESEARCH
Vol. 3 (12)
p. 2682-2686
1997

14) Nakashima et al.
"Human MCAF gene transfer enhances the metastatic capacity of a mouse cachectic adenocarcinoma cell line in vivo"
PHARMACEUTICAL RESEARCH
Vol. 12 (11)
p. 1598-1604
1995

15) Kruger et al.

Fractalkine – a strange attractor in the chemokine landscape

Dendrograms depicting evolutionary relationships in the growing array of chemokines and their receptors are beginning to resemble elegant Mandlebrot patterns – those eerily beautiful, iterative and self-referential tracings that have been used to describe the geometry of everything from cauliflowers to continents. Thus, it seems fitting to invoke such a complex metaphor to describe the latest layer in the baroque system controlling leukocyte trafficking, inflammation and infectious processes. 'Fractalkine' therefore seems an appropriate name for a novel class of chemokine that adds a new twist to models of cellular trafficking and immune regulation[1].

Prior to fractalkine, chemokines had been thought of as soluble cytokines bearing a variation of a conserved cysteine structural motif: 'CC', 'CXC' or 'C', depending on the number and spacing of the N-terminal cysteine residues[2,3]. Fractalkine is doubly novel in sporting both a CX_3C motif and being encoded as a membrane-bound molecule, with the chemokine domain perched atop a long mucin-like stalk. This 'chemokine-on-a-stick' strategy allows the chemokine domain of fractalkine to be 'presented' on the surface of a cell to act upon another cell bearing the apropriate receptor. So far, we know that fractalkine can be induced markedly on primary cultured human endothelial cells, and that cell-bound fractalkine promotes the adhesion of monocytes and T cells *in vitro*. Cell-bound fractalkine can also be cleaved (via a syndecan-like cleavage motif proximal to the membrane) and released as a shed glycoprotein that has chemoattractant effects on monocytes and T cells.

Overall, these data suggest the following model: (1) fractalkine is upregulated on the endothelium; (2) this induces adhesion of monocytes and T cells (perhaps by effecting the transition of selectin-rolling cells to firm adhesion via the integrins[4]); and (3) the response might be downregulated by cleavage of fractalkine from the cell. This mechanism would explain the long-held notion that chemokines are generally presented by extracellular components of the endothelium[5], lest they be washed away by blood flow, or bound and cleared by a promiscuous chemokine receptor on the surface of erythrocytes. Fractalkine solves many mysteries of specificity and regulation of the presentation process with its intrinsic structural features.

Other functions are possible, even likely, for this new chemokine. Its broad pattern of mRNA expression may suggest roles beyond directing the migration of mature leukcoytes at the endothelium. Its presumed presence in organs not usually associated with leukocytic infiltration is compelling. The expression of fractalkine (and other chemokines) in multiple tissues, and at different times in development, suggests differential roles exploiting the fundamental chemokine property of inducing cell migration. During development, this property might be useful in morphogenesis; in the mature animal it could be exploited in leukocyte motility. Other roles could include tissue integrity, repair and regeneration. In all of these situations, the importance of both the cell-surface and shed forms of the molecule could be envisaged: the former regulating cell–cell interactions, the latter forming local chemoattractant gradients. Immunochemical and genetic experiments will soon open up these areas.

The structure of fractalkine offers other intriguing questions. Does this molecule blur the traditional distinction between adhesion molecules (the selectins, integrins, etc.) and chemoattractants? That is, does the fractalkine structure directly mediate an adhesive interaction, rather than inducing downstream activation of other adhesion molecules? This possibility is tantalizing, given that many classical adhesion molecules exploit mucin domains. Furthermore, there is a surprising degree of conservation in the transmembrane and intracellular domains of fractalkine between mice and humans. There are no clearly recognizable signaling motifs in these regions, but this conservation may suggest other functions beyond tethering. Finally, will other CX_3C chemokines be uncovered; for example, are there new fractalkines regulating the adhesion and migration of granulocytes? As in the case of lymphotactin (the only 'C' chemokine identified to date, nearly four years after its initial description), obvious experiments have not yet yielded other chemokines-on-a-stick.

Fractalkine represents a key part of the process of leukocyte trafficking, a complex system that determines the balance between health and disease. By definition, complex systems are large, unstable and difficult to regulate. This is exactly the case with leukocyte trafficking. The process, required in all higher vertebrates to maintain immune function, seems paradoxically routine yet inherently chaotic. Its dysregulation is at the heart of many human miseries. So, just as geometric fractals record what happens at the boundaries between order and chaos, fractalkine may provide clues to a system where small changes can effect large, undesired consequences. It may represent a critical juncture, a control point that can become dysfunctional (perhaps by inappropriate endothelial expression, or by a failure to cleave due to mutations in the fractalkine stalk or a defect in the cleaving enzyme), resulting in a normally self-resolving inflammatory response degenerating into a persistent inflammatory or autoimmune disease. Although these possibilities represent new layers of complexity, at the same time they offer new targets for clinical intervention. Clearly, the presence of fractalkine reflects an evolutionary need – the sheer numbers of chemokines and their receptors tell us that feedback and iteration are the soul of this system. Its elucidation should do much to enhance understanding of the molecular events controlling cellular trafficking at the endothelium and beyond.

Thomas Schall (schall@dnax.org) is at DNAX Research Institute, 901 California Ave, Palo Alto, CA 94304, USA.

References

1 Bazan, J.F., Bacon, K.B., Hardiman, G.B. *et al.* (1997) *Nature* 385, 640–643

2 Strieter, R.M., Standiford,T.J., Huffnagle, G.B., Colletti, L.M., Lukacs, N.W. and Kunkel, S.L. (1996) *J. Immunol.* 156, 3583–3586

3 Premack, B.P. and Schall, T.J. (1996) *Nat. Med.* 2, 1174–1178

4 Butcher, E.C. and Picker, L.J. (1996) *Science* 272, 60–66

5 Webb, L.M.C., Ehrengruber, M.U., Clark-Lewis, I. *et al.* (1993) *Proc. Natl. Acad. Sci. U. S. A.* 90, 7158–7162